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Multisensory mental imagery of *fatigue* in patients with multiple Sclerosis. Preliminary evidence from a fMRI study

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ABSTRACT

Fatigue, defined as a subjective lack of physical and/or mental energy, is a clinical symptom highly characterizing multiple sclerosis (MS). The present study utilized a novel approach to the study of fatigue, examining first person-mental imagery of the symptom. Eighteen right-handed patients with MS (14F, 4 M, mean age 45.8 ± 8.15 years) were evaluated and were compared to nineteen healthy controls (10F, 9 M, mean age 43.15 ± 8.34 years) Patients were all in relapsing remitting form and no patient had presented relapses in the 6 months prior to inclusion in the study. We evaluated their behavioral performance and fMRI activations. We used an fMRI paradigm used to trigger first person-mental imagery of *fatigue*, through short sentences describing the principal manifestations of *fatigue*. Participants were asked to imagine the corresponding sensations (Sensory Imagery, SI). As a control, they had to imagine the visual scenes (Visual Imagery, VI) described in short phrases. They made a vividness rating by pressing the corresponding button.

Behaviorally, we found that patients' mean scores at the Multidimensional Fatigue Symptom Inventory for the general scale, physical scale, and mental scale were significantly higher than healthy controls ($p = 0.05$, $p = 0.002$, $p = 0.006$ respectively), but not for the emotional scale and for vigor scale ($p = 0.207$, n.s., $p = 0.06$, n.s.). In the imagery fMRI task, patients were significantly slower (mean reaction times and standard deviation: 2.24 s ± 0.33) than controls (mean reaction times and standard deviation: 1.918 s ± 0.455) for the SI task ($Z=-2.058$, $p = 0.040$), while no significant difference was found for the VI task.

Regarding brain mapping, our main result is a group by task interaction. The SI task (vs. VI task) in healthy controls (relative to patients) increased activation in the left inferior parietal lobule. These preliminary results indicate that fatigue is related to dysfunctions in higher-order aspects of motor control, given the role of the posterior parietal lobe in motor planning and multisensory integration.

1. Introduction

Fatigue affects approximately 70–90 % of patients with Multiple Sclerosis (MS) (Schapiro, 2002; Kobelt et al., 2017), with more than 50 % of persons with MS reporting fatigue as their most disabling symptom (Schapiro, 2002). Nevertheless, it is often an underestimated symptom, as it is one of the so-called invisible symptoms. This is in striking contrast with the strong interference fatigue can cause with patients' social activities and work capacity thus exerting an impact on the persons' quality of life. The exact pathophysiological mechanism of fatigue in MS is still unknown (e.g., Zimek et al., 2023; Maier et al., 2023; Sedaghati et al., 2023). This is likely related to the fact that fatigue has multiple different underlying mechanisms (for a review see Manjaly et al., 2019). The major characterization of fatigue is a persistent and heavy physical and/or mental tiredness which has multiple dimensional factors, namely central, peripheral, behavioural and psychological ones (DeLuca, 2005). Clinically, fatigue can be defined as "*a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with*

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usual and desired activities" (p. 2, Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). Recently it has been pointed out that fatigue can significantly affect postural control by impairing the ability of the central nervous system to modulate sensory inputs and coordinate motor responses (Sedaghati et al., 2023).

While behaviorally, a plenty of questionnaire and cognitive or motor tasks increasing in their difficulty levels has been developed and used to quantify fatigue, few paradigms have been designed to study fatigue at neural level by using neuroimaging techniques (e.g., Bertoli and Tecchio, 2020). Studying fatigue on a functional neuronal level might be important/beneficial to get a more comprehensive view on pathophysiologic processes underpinning fatigue in MS. Studies using the resting state technique showed that the resting state connectivity in MS patients experiencing fatigue (vs. healthy controls) was stronger in the posterior cingulate cortex, and reduced in the anterior cingulate cortex (Bisecco et al., 2018), indicating that fatigue impacts on non-motor networks. In another resting state study, it was reported that the alterations of the functional connectivity in temporo-parietal areas correlates with increased fatigue levels (Buyukturkoglu et al., 2017; Engstrom et al., 2013), suggesting that perception plays a pivotal role in fatigue. In Hidalgo de la Cruz et al. (2018)'s study it was reported that functional connectivity between the thalamus and middle frontal gyrus, sensorimotor network, precuneus, insula, and cerebellum correlated with global MFIS. Lastly, Tijhuis et al. (2021) found that greater fatigue levels in MS patients was correlated to less dynamic connectivity between the basal ganglia and the cortex, and that increased fatigue could relate to lower dynamics of these connections. Active fMRI studies involving the presentation of motor demanding tasks showed that patients reporting fatigue (vs. those who did not) demonstrated greater activation of the right premotor area, of the putamen and the dorsolateral prefrontal cortex, which are involved in motor planning and conscious motor adaptation (Specogna et al., 2012). On the contrary Filippi et al. (2002) presented patients with a finger tapping task performed with the right hand, and found that patients reporting fatigue (vs. those who did not) had less activation in the right precuneus, right rolandic operculum, right cerebellar hemispheres, and in the left middle frontal gyrus, and left thalamus. Rocca et al. (2016) presented MS patients with a motor task and found that patients reporting fatigue (vs. those who did not and heathy controls) had reduced activations of the left middle temporal gyrus, left supplementary motor area (SMA), bilateral superior frontal gyrus, left postcentral gyrus and basal ganglia regions.

Active fMRI studies involving the presentation of highly demanding cognitive tasks showed that patients (vs. healthy controls) were significantly slower (indicating fatigue) in solving a symbol digit modality test assessing psychomotor speed and had an increased activation in the basal ganglia, frontal areas, parietal regions (precuneus and cuneus), thalamus and the occipital lobes (see also Tartaglia et al., 2008).

An additional measure of fatigue–related fMRI changes involves explicit, first person, multisensory mental imagery of fatigue related sensations. In a previous fMRI study on healthy participants, we asked them to explicitly imagine a series of sensations (Sensory Imagery, contrasted with a control task −Visual Imagery) according to the items of the "Multidimensional Fatigue Symptom Inventory (MFSI)" (Stein et al., 1998). We found that Sensory Imagery (vs. Visual Imagery) activated the left precuneus, the superior temporal sulcus and the inferior frontal gyrus which are involved in mental imagery of first-person perspective taking and multisensory integration area (Tomasino et al., 2022). Based on these results, in the present study, we aimed at investigating the mental representation of fatigue-related sensations in patients with MS. The choice of this mental imagery task is based on the strict parallelism at neural level between imagination and perception (Ehrsson et al., 2003; Stippich et al., 2002; Tomasino et al., 2005). As there is no fMRI study on imagery of fatigue-related sensation imagery in MS, we did not formulate hypotheses on which brain structures might show (if any) differential activations when compared to healthy controls. However, based on the literature on the above-mentioned functional parallelism between perception and multisensory imagery, we expected to find altered activations in areas recruited by mental imagery for sensory imagery (e.g., Olivetti Belardinelli et al., 2004; Olivetti Belardinelli et al., 2009; McNorgan, 2012; Stein et al., 1998) in patients with MS compared with healthy controls. Specific hypothesis about whether it in these areas we will find hyper- or hypo-activations it is difficult to formulate as the literature above could not be used to base our specific expectation since our mental imagery paradigm is new and not directly comparable with previous literature. Indeed the present study is exploratory.

2. Methods and Materials

2.1. Participants

Eighteen right-handed (Oldfield, 1971) patients with MS 14F, 4 M, mean age 45.8 ± 8.15 years) participated in the study. Mean values and distributions of demographic and clinical data, separately for patients and healthy controls are reported in Table 1 and patients' individual clinical and demographic data are reported in Supplementary Table 1). Inclusion criteria for MS patients were: i) age between 18 and 65 years; ii) diagnosis of relapsing-remitting MS following revised McDonald criteria (Thompson et al., 2018); iii) expanded disability status scale (EDSS) < 2.5 at enrolment; iv) patients on disease-modifying drug for at least 1 year; v) clinically relevant fatigue (score on Fatigue Severity Scale > 4); vi) body mass index (BMI) between 19 and 30 kg/m^2. Exclusion criteria were: i) renal failure (estimated glomerular filtration rate with Cockroft-Gault < 60 ml/min); ii) hepatic failure; iii) Diabetes mellitus; iv) pregnancy and lactation; v) known thyroid dysfunction; vi) Alcohol abuse; vii) eating disorders; viii) treatment with anti-depressive or hypnotic drugs; ix) relapses of MS in the last 6 months; x) steroid treatment in the last 6 months; xi) new MRI demyelinating lesions in the previous 6 months. All patients had normal or corrected- to-normal vision.

Patients' data were contrasted to those of a group of healthy subjects (10F, 9 M, mean age 43.15 ± 8.34 years) which had been studied in a previous work by our group (Tomasino et al., 2022). All subjects were native speakers of Italian with comparable levels of education. All subjects had normal or corrected- to-normal vision and reported no history of neurological illness, psychiatric disease, or drug abuse according to their responses on self-report measures. Patients and controls were matched for age (Mann-Whitney Test, $Z = -0.96$, $p = 0.346$, n.s.) and for gender (χ^2 Test, $\chi^2 = 2.565$, $p = 0.170$, n.s.).

Participants compiled the "Multidimensional Fatigue Symptom Inventory (MFSI)", which is an 83-item self-report measure designed to assess the principal manifestations of fatigue. Items are rated on a 5-point scale, indicating how true each statement was for the respondent during the previous week (0 = not at all; 4 = extremely). The MFSI takes about 10 min to be completed. Higher scores indicate more fatigue. Following the scoring (Stein et al., 1998) for the empirically

Table 1
Mean values and distributions of demographic or clinical data, separately for patients and healthy controls.

	Patients	Healthy controls
Age (max/min, median)	63/29, 47	56/28, 45
Gender	14F, 4 M	10F, 9 M
Yrs. from diagnosis (max/min, median)	25/2, 9	–
EDSS (max/min, median)	2/1, 1.5	–
Therapy	3 Teriflunomide; 7 Dimethyl fumarate; 4 Glatiramer acetate; 3 Interferon β-1a; 1 Cladribine	–
MRI characteristics (median, IQR)	T2 lesion load (ml) 2.498 (5.92)Total number of T2 lesions 14.5 (8.5)	

derived scales, we derived scores for a general scale (the sum of items like I feel pooped; I am worn out, I feel run down) in addition to a physical scale, an emotional scale, a mental scale and a vigor scale. There is no Italian version of the MFSI. An English expert checked the translation to Italian of the 83 items and then performed the Back translation as this type of study requires.

Subjects were all monolingual native speakers of Italian. The study was approved by the by Friuli Venezia Giulia Unique Regional Ethical Committee (CEUR-2020-SPER-124). Written informed consent was obtained from each adult participant.

2.2. Experimental design

2.2.1. Stimuli, task and experimental paradigm

Stimuli and task were validated in an fMRI study on healthy participants previously published by our group (Tomasino et al., 2022). Stimuli related to fatigue sensations were short sentences belonging to the MFSI (Stein et al., 1998), which were contrasted to a list of items describing a visual scene of comparable length as the body sensation items ($t(41) = -1.92$, $p > 0.05$, see Tomasino et al., 2022).

Participants were asked to silently read the short phrases and to imagine in a first person the sensations (Sensory Imagery, SI, 7 blocks of task, 15 s) or the visual scenes (Visual Imagery, VI, 7 blocks of task, 15 s) pseudo randomized in order of appearance, to make a vividness rating on a 4-level scale [1–4, from poor vividness (1) to vivid as real (4)] by pressing the corresponding button. Instructions asked participants to press the corresponding button at the time they reached a decision on the vividness level of their mental image. Vividness is defined as clarity, liveliness of a mental image. Blocks of tasks were alternated with fifteen blocks of rest (12.5 s). Each block included 4 short phrases. Each short phrase (n = 56, 28SI, 28 VI) had a duration of 3750 ms. Items were balanced as each of the items belonging to the derived subscales (general, physical, emotional, and mental as well as in part vigor[2]) obtained from Stein et al.'s (1998) factor analysis were included.

Visual stimulation was generated by using Presentation (Neurobehavioral Systems, Inc., Berkeley, CA, USA, https://www.neurobs.com) and presented by using the VisuaStimDigital (Resonance Technology Inc., Los Angeles, CA, USA) goggles system. Responses were given by pressing 4 keys of an MRI Compatible Keypad (Resonance Technology Inc., Los Angeles, CA, USA) with the fingers of the right hand. Subjects practiced the task outside the scanner, prior to the magnetic resonance experiment, and utilized the dominant hand to respond.

2.2.2. MRI Acquisition

Images were acquired using a 3 T Achieva MR whole-body scanner (Philips, The Netherlands) with a standard 8 channel head coil. High-resolution anatomical images were acquired using a 3D T1-weighted Turbo-Gradient Echo sequence (TR: 8.388 ms, TE: 3.85 ms, Voxel Size: 1 mm × 1 mm, Thickness: 1 mm, Number of Slices: 190, Field of View: 240 mm x 190 mm x 240 mm, Acquisition Matrix: 240 × 240, Flip Angle: 8°). Fluid-attenuated inversion recovery (FLAIR) sequence (TR: 4600 ms, TE: 325 ms, TI=1650 ms, Voxel Size: 0,98 mm × 0,98 mm × 1 mm, Thickness: 1 mm, NEX=2 Number of Slices: 280, Field of View: 250 mm x 250 mm, Acquisition Matrix: 256 × 256, Flip Angle: 90°). Functional images were obtained using a T2*-weighted Gradient-Echo Echo-Planar Imaging EPI sequence (TR: 2500 ms, TE: 35 ms, Voxel Size: 1.797 mm × 1.797 mm, Thickness: 3 mm, Number of Slices: 29, Field of View: 230 mm × 88.33 mm × 230 mm, Acquisition Matrix: 128 × 128, Flip Angle: 90°, Number of Volumes: 308). The neuroradiologist assured that this field of view used was sufficient to cover the brain in all the patients. Slices were acquired in the axial plane, parallel to the anterior commissure/posterior commissure (ACPC) line. The total scanning time was 15 min (7 min the fMRI task plus the anatomical T1 acquisition).

2.3. Data analysis

2.3.1. Behavioral data

Behavioral performance was analyzed using SPSS 21.0 (SPSS, Inc., Chicago, IL) on subjects' reaction times and vividness by performing a Mann-Whitney Test with, as factors, the group (patients, healthy controls) and the task (SI, VI).

Scores (0 = not at all; 4 = extremely true) for the scales derived from the Multidimensional Fatigue Symptom Inventory (MFSI) were compared by performing a one-way multivariate analysis of variance (one-way MANOVA) to determine whether there were any differences between independent groups (patients vs. healthy controls) on more than one continuous dependent variable (the MFSI scale: general scale, physical scale, an emotional scale, a mental scale and a vigor scale). In addition, we calculated the total score, which is the sum of all the responses to the 83 items of the MFSI, and compared this measure between groups.

2.3.2. MRI data processing

FMRI preprocessing and statistical analysis were performed using MATLAB18r (The Mathworks, Inc., Natick, MA, USA) and SPM12 (Statistical Parametric Mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, U.K. www.fil.ion.ucl.ac.uk/spm). The first four volumes of each functional dataset were discarded from analysis in order to allow for T1 equilibration effects.

We spatially realigned the images to the reference volume (i.e., the now first/previously fifth acquired volume) and then co-registered to the mean EPI image. The mean EPI image was normalized to the standard single subject template in MNI space. A Gaussian kernel of 6 mm full-width half-maximum was used for smoothing to meet the statistical requirements of the theory of Gaussian fields according to the General Linear Model employed in SPM and to compensate for interindividual variability in macro- and micro anatomical structures across subjects (Friston et al. 1995a; Friston et al. 1995b).

For this experiment, three event-types were defined and then used as conditions for the model specification: (1) SI, (2) VI, (3) resting, "Rest". A General Linear Model (GLM) was thus applied to each voxel of the functional dataset. A temporal high-pass filter of 1/128 Hz and linear trend removal were employed. The three translation and the three rotation movement parameters obtained from the initial spatially realignment were included as further regressors.

Specific effects were assessed by applying appropriate linear contrasts of the parameter estimates of the two experimental conditions and the baseline, resulting in t-statistics for each voxel. The set-statistics were then Z- transformed to statistical parametric maps (SPM{Z}) of differences between the experimental conditions and between the experimental conditions and the baseline. SPM{Z} statistics were interpreted in light of the probabilistic behavior theory of Gaussian random fields (Friston et al., 1995a; Friston et al., 1995b). For each subject, we calculated the following contrast images: the simple contrasts tasks (SI-rest and VI-rest), and the main effect of the task [SI–VI] and [VI-SI].

For second-level random effects analyses, contrast images obtained from individual participants were entered into a two-sample *t*-test to create a statistical parameter map of the t-statistics, indicative of significant activations specific to the contrasts SI-VI and VI-SI and simple contrast SI-rest and VI-rest at the group level (patients vs. healthy controls and vice versa). At the second level we also performed a conjunction null analysis (Friston et al., 1999), showing the common activated network for both tasks ([SI-baseline]_patients ∩ [SI-baseline]_controls) and ([VI-baseline]_patients ∩ [VI-baseline]_controls) using a threshold

[2] in the vigor subscale items are framed in a positive way (i.e., "I feel energetic"). To avoid the simulation of a "positive" sensation we presented them as reversed form, e.g, I feel energetic –> I feel little energetic (e.g., in Italian "*mi sento poco energico*").

of p < 0.05, FEW corrected at the voxel level.

We used a threshold of $p < 0.05$, corrected for multiple comparisons at the cluster level (using family-wise error (FWE)), with a height threshold at the voxel level of $p < 0.001$, uncorrected. Furthermore, the localization of these individual activations peaks was confirmed by the SPM Anatomy toolbox 3.0 (Eickhoff et al., 2005).

For the quantification of T2-hyperintense lesion load, lesions were segmented by the lesion prediction algorithm (Schmidt, 2017, Chapter 6.1) as implemented in the LST toolbox (version 3.0.0) (https://www.statistical-modelling.de/lst.html) for SPM12. Results are shown in Table 1.

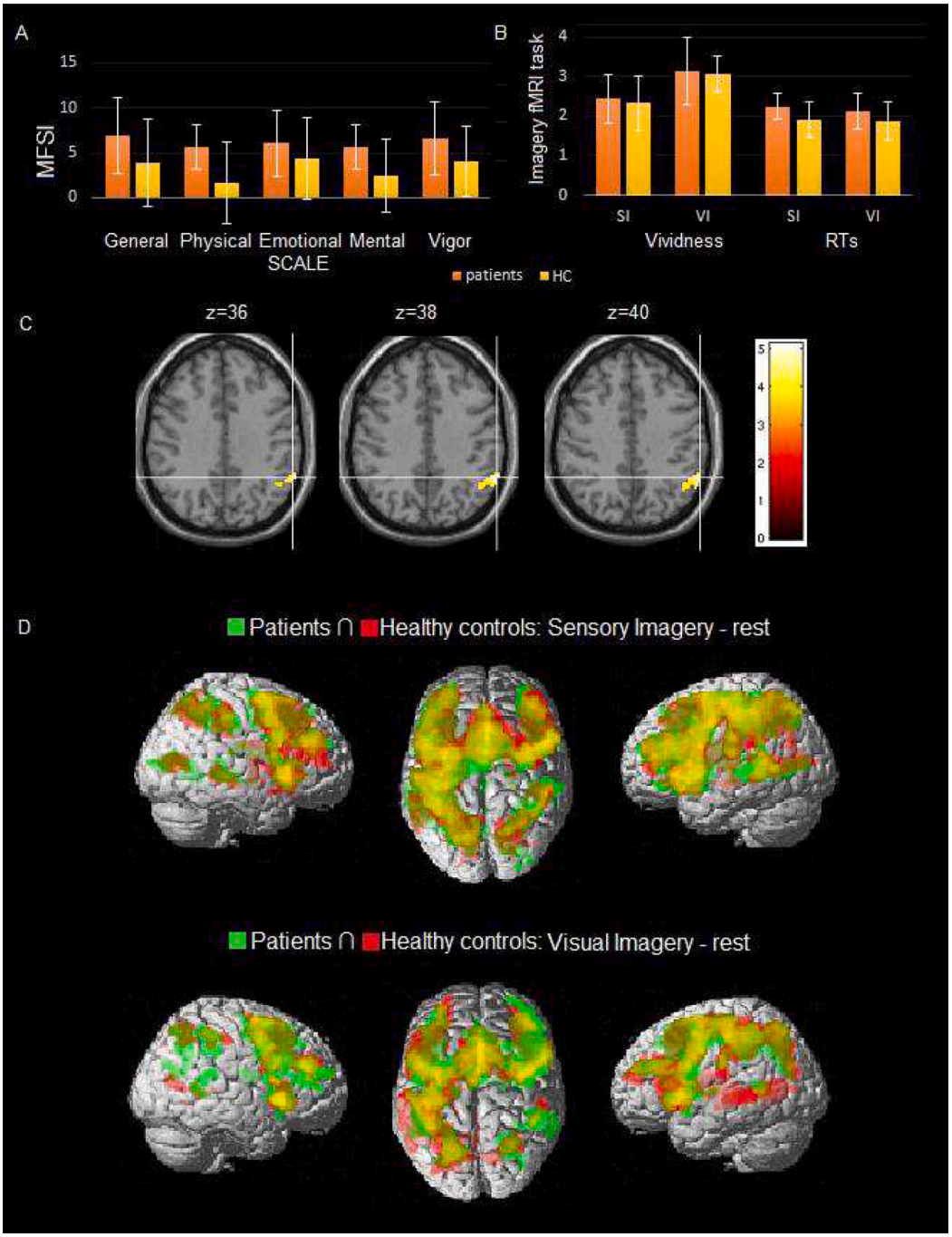

Fig. 1. (A) Patients' and healthy controls (HC) sum of scores (error bars represent standard deviations) at each subscale of the MFSI. (B) Patients' and healthy controls (HC) mean vividness ratings (error bars represent standard deviations) and mean Reaction Times (RTs, seconds) at the Imagery fMRI task on Sensory Imagery (SI) and Visual Imagery (VI) (error bars represent standard deviations). (C) The activation clusters in the left inferior parietal lobe differentially recruited by the task x group interaction, namely by HC (as compared to patients) in the SI (as compared to VI) ($p < 0.05$, corrected at the cluster level see Table 2) are displayed on a T1 brain template provided by SPM12. Colour bar represents t value. (D)Task related network for patients and controls and their shared activation in yellow are plotted by using the "Surface Rendering in SPM". (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

3.1. Behavioural data

3.1.1. Multidimensional fatigue Symptom Inventory (MFSI)

According to the MFSI, higher scores indicate more fatigue experienced during the previous week. Sum of scores for general scale, physical scale, and mental scale were significantly different between patients and healthy controls (p = 0.05, p = 0.002, p = 0.006 respectively, see Fig. 1A, left side of the panel), but not for the emotional scale and for vigor scale (p = 0.207, n.s., p = 0.06, n.s.).[3]

In general, the sum of all the responses to the 83 items of the MFSI was very high for patients (76.65 ± 34.71) as compared to controls (47.89 ± 28.79, $p < 0.005$).

3.1.1.1. Imagery fMRI task: Reaction times. RTs significantly differ between patients (mean ± standard deviation: 2.24 ± 0.33 s) and controls (mean ± standard deviation: 1.918 ± 0.455 s) for the SI task (Z=-2.058, p = 0.040), while no significant difference was found for the VI task (patients, mean ± standard deviation: 2.11 ± 0.44 s; controls, mean ± standard deviation: 1.86 ± 0.47 s) (Z=-1.303, p > 0.05, n.s. see Fig. 1B, right side of the panel).

3.1.1.2. Imagery fMRI task: Vividness. The ratings did not significantly differ between patients and controls neither for the SI tasks (Z = −0.22, p > 0.05, n.s.) nor for the VI task (Z = −0.51, p > 0.05, n.s., see Fig. 1B, right side of the panel).

3.2. fMRI data

3.2.1. Group comparisons (patients vs. Healthy controls of differential task effects)

The main result is an interaction of group by task (see Table 2 and Fig. 1). The Sensory Imagery task (relative to Visual Imagery task) in healthy controls (relative to patients) increased activation in the left inferior parietal lobule. The reverse contrast, i.e., Sensory Imagery task (relative to Visual Imagery task) in patients (relative to controls) failed to show any suprathreshold activation.

3.2.2. Group comparisons (patients vs. Healthy controls of simple contrasts SI-Rest; VI-Rest)

The Sensory Imagery task (relative to rest) in patients (relative to healthy controls) activate the right angular gyrus and the posterior and the anterior cingulate gyri. The reverse contrast, i.e., Sensory Imagery task (relative to rest) in healthy controls (relative to patients) failed to show any suprathreshold activation.

The Visual Imagery task (relative to rest) in patients (relative to healthy controls) and the same contrast in in healthy controls (relative to patients) failed to show any suprathreshold activation.

To further address the activation in the angular gyrus and cingulate cortex we run an additional analysis by entering into a two-sample *t*-test the contrast images obtained from individual participants specific to rest-SI and VI-rest at the group level (patients vs. healthy controls and vice versa). We found that rest (relative to SI) in controls (relative to patients) activated the angular gyrus (x = 58 y = -50 z = 22, T=5.65 k = 157) and cingulate cortex (x = 6 y = 34 z = 8, T=5.09 k = 475 and x = 2 y = -52 z = 28, T=5.35 k = 326). In addition, rest (relative to VI) in controls (relative to patients) activated the angular gyrus (x = 58 y = -54 z = 24, T=6.30 k = 150).

[3] We re-run the analysis by excluding patients (n=3, case n#4, #5, #17) who were treated with interferon beta, which has as side effect the development of fatigue. Results did not change. Sum of scores for general scale, physical scale, and mental scale were significantly different between patients and healthy controls (p = 0.023, p = 0.002, p = 0.004 respectively), but not for the emotional scale and for vigor scale (p = 0.182, n.s., p=.078, n.s.).

Table 2
Brain regions showing significant relative increases of BOLD response associated with each comparison of interest.

Side	Region	MNI coordinates			T	Size (k_E)
		x	y	z		
Healthy Controls – Patients: Sensory imagery – Visual imagery						
LH	Inferior parietal lobule (PFm)	−58	−50	38	5.15	129
Patients – Healthy Controls: Sensory imagery – Visual imagery						
–	–	–	–	–	–	–
Patients – Healthy Controls: Sensory imagery – rest						
RH	Angular gyrus	58	−50	22	4.98	150
M	Posterior cingulate gyrus	−2	−52	24	4.96	356
M	Anterior cingulate gyrus	0	40	4	4.91	283
Healthy Controls – Patients: Sensory imagery – rest						
–	–	–	–	–	–	–
Patients – Healthy Controls: Visual imagery – rest						
–	–	–	–	–	–	–
Healthy Controls – Patients: Visual imagery – rest						
–	–	–	–	–	–	–

For each region of activation, the coordinates in MNI space are given referring to the maximally activated focus within an area of activation as indicated by the highest T-value.
LH/RH=left/right hemisphere, M=medial; Size = number of voxels in a cluster. All the activations are significant at P<0.05 (corrected for multiple comparisons at the cluster level, height threshold P<0.001, uncorrected).

3.2.3. Task related network

3.2.3.1. The sensory imagery (SI) vs. Rest. The network of areas activated by the SI (relative to rest) in patients included bilaterally the calcarine cortex, the superior temporal gyrus, the inferior and superior parietal lobe, the supplementary motor area, the left inferior frontal gyrus and the right insula. The conjunction analysis performed on the SI task in patents and controls showed that this network in patients was very similar to that of healthy controls (see Table 3 and Fig. 1).

3.2.3.2. The visual imagery (VI) vs. Rest. The network of areas activated by the VI (relative to rest) in patients included bilaterally the middle temporal gyrus, the superior parietal lobe, the right superior temporal gyrus, the right supramarginal gyrus, the right inferior parietal lobe, the right middle frontal gyrus and the right inferior frontal gyrus, the supplementary motor area, the left precentral gyrus, the right insula, and the right putamen. The conjunction analysis performed on the VI task in patents and controls showed that this network was very similar to that of healthy controls (see Table 3 and Fig. 1).

4. Discussion

Using fMRI in patients with MS, we investigated the neural correlates of mental imagery of *fatigue* related multisensory sensations. To do so, patients imagined the corresponding content of items from the Multidimensional Fatigue Symptom Inventory (MFSI) designed to assess the principal manifestations of *fatigue* (Stein et al., 1998). This fMRI task was validated in a previous study of our group on healthy volunteers (Tomasino et al., 2022). Overall, the SI (vs. rest) network was very similar to that of healthy controls, as shown by the conjunction analyses. It included bilaterally the calcarine cortex, the STG, the IPL and SPL, the

Table 3
Brain regions showing significant relative increases of BOLD response associated with each comparison of interest for Patients.*

Side	Region	MNI coordinates			T	Size (k_E)
		x	y	z		
Patients: Sensory imagery – rest						
RH	Calcarine cortex	30	−68	10	5.56	521
LH	Calcarine cortex	−18	75	15	5.23	
RH	Superior temporal gyrus	46	–32	−2	5.54	274
LH	Superior temporal gyrus	−47	56	15	4.01	
RH	Inferior parietal lobe	30	−54	50	6.15	1379
RH	Superior parietal lobe	14	−64	58	5.60	
M	Supplementary motor area	−6	4	60	8.09	22,526
LH	Inferior frontal gyrus	−30	28	−4	8.00	
LH	Inferior parietal lobe	−34	−40	46	7.86	
RH	Superior parietal lobe	14	−64	58	6.80	
RH	Insula	46	18	−4	6.66	
Patients: Visual imagery – rest						
RH	Superior temporal gyrus	60	−46	12	4.48	201
RH	Middle temporal gyrus	58	−48	4	4.26	
LH	Middle temporal gyrus	−52	−52	6	4.76	107
RH	Supramarginal gyrus	44	−40	40	5.88	433
RH	Inferior parietal lobe	48	−38	50	5.77	
RH	Superior parietal lobe	20	−66	52	5.33	652
LH	Superior parietal lobe	−19	−73	54	5.21	
RH	Middle frontal gyrus	40	38	24	8.17	14,929
RH	Inferior frontal gyrus	54	16	−2	8.10	
M	Supplementary motor area	−6	4	58	7.98	
LH	Precentral gyrus	−42	−2	40	7.42	
RH	Insula	42	16	−4	7.58	
RH	Caudate nucleus	18	6	16	5.46	162
Patients ∩ Healthy Controls: Sensory imagery – rest						
RH	Calcarine cortex	12	−70	10	4.85	294
LH	Calcarine cortex	−14	−78	8	4.96	256
LH	Middle temporal gyrus	−50	48	0	5.15	595
RH	Superior temporal gyrus	46	−30	−2	5.47	119
RH	Middle temporal gyrus	46	−40	2	4.96	
RH	Inferior parietal lobe	30	−54	48	5.35	618
RH	Supramarginal gyrus	46	–32	42	4.96	
RH	Superior parietal lobe	16	−64	58	4.7	
M	Supplementary motor area	−6	4	60	8.09	13,340
LH	Inferior frontal gyrus	−30	28	−4	8.09	
RH	Inferior frontal gyrus	48	13	−4	7.78	
LH	Inferior parietal lobe	−34	−40	46	7.50	
Patients ∩ Healthy Controls: Visual imagery – rest						
M	Supplementary motor area	4	6	52	6.48	6933
LH	Superior parietal lobe	−18	−70	52	6.45	
LH	Precentral gyrus	−42	−2	40	6.3	
RH	Insula	44	14	0	6.77	590
RH	Inferior frontal gyrus	54	18	−2	6.40	
RH	Precentral gyrus	60	10	16	4.44	
LH	Middle frontal gyrus	–33	29	33	4.40	
LH	Superior parietal lobe	−19	−73	54	4.23	
LH	Inferior parietal lobe	−28	−76	33	4.02	
RH	Middle frontal gyrus	40	36	28	6.80	292

For each region of activation, the coordinates in MNI space are given referring to the maximally activated focus within an area of activation as indicated by the highest T-value.
LH/RH=left/right hemisphere, M=medial; Size = number of voxels in a cluster. ∩ = conjunction analysis.
All the activations are significant at $P<0.05$ (corrected for multiple comparisons at the cluster level, height threshold $P<0.001$, uncorrected).
* MNI coordinates for simple contrasts for healthy controls are not reported as they have been published in Tomasino et al. (2022).

SMA, the left IFG and the right insula (see Tomasino et al., 2022). Similarly, there was a shared network between patients and controls for the VI (vs. rest) task. It involved bilaterally the MTG, the SPL, the right STG, the right SMG, the right IPL, the right middle frontal gyrus and the right IFG, the SMA, the left precentral gyrus, the right insula, and the right putamen (see Tomasino et al., 2022).

Prior to fMRI scanning patients completed the MFSI. We found that general scale, physical scale, and mental scale were significantly higher for patients as compared to healthy controls, while scores at the emotional scale and at the vigor scale were comparable to controls. According to the MFSI, higher scores indicate more fatigue experienced during the previous week for the relative measured scale. In addition, these data show that in our MS patients fatigue symptoms dissociated from the emotional experience and from vigor index, as we found a dissociation between their scores. It is accepted that fatigue and emotion-related changes are interconnected in the pathology of MS (e.g., Pagnini et al., 2014; Raimo et al, 2021). We could only speculate that our result concerning the emotion-related subscale is then somewhat counterintuitive; as to the vigor subscale it could be related to the items belonging to the vigor scale are phrased in a positive sense (e.g., I feel calm; I feel energetic; I feel refreshed as examples for the vigor scale), while the items belonging to the other subscales are phrased as phrases expressing the symptoms of fatigue (I feel heavy legs; My muscles ache).

Interestingly, a group by task interaction was found both at behavioral level and at neural level: healthy controls were significantly faster, as compared to patients, in the SI task, as compared to VI task. A possibility is that patients were overall slower in to think about the strength of the sensation – rather than it being a sign of fatigue (indeed they were not explicitly instructed to make a decision as quickly as possible, but only to press the button once the decision was made), as they were also a little slower compared to healthy controls in the VI task, though not statistically significant.

At neural level, the SI task (relative to VI task) in healthy controls (relative to patients) increased activation of the left inferior parietal lobule. On the contrary, the reverse contrast, i.e., SI task (relative to VI task) in patients (relative to controls) failed to show any suprathreshold activation. This differential activation is not free of the difficulties in the interpretability of increases vs decreases. According to the neuroimaging literature abnormal activation patterns are indeed found, among other areas, in the parietal lobes, in fatigued patients (e.g., Filippi et al., 2002; Jaeger et al., 2019; Roelcke et al., 1997; Tartaglia et al., 2004; Wilting et al., 2016). Both increases and decreases in activation are found. For instance, DeLuca et al. (2008) used an fMRI processing speed paradigm (modified Symbol Digit Modality Test) in MS patients and healthy controls. The two groups had comparable performance accuracy, despite being significantly different in terms of reaction terms (patients were slower, indicative of fatigue). At neural level, an increased activation in the basal ganglia, frontal areas, parietal regions (precuneus and cuneus), thalamus and the occipital lobes was found in patients, as compared to controls. Jaeger et al., 2019 performed a resting-state fMRI study and administered a fatigue severity scale involving MS patients experiencing fatigue, those non-fatigued and healthy controls. They found that the caudate nucleus had a reduced functional connectivity sensorimotor and frontal, parietal, and temporal cortex regions, which are nodes of the frontopatietal attention network, in patients with MS-related fatigue compared to MS patients without fatigue and HC. Interestingly, there was a positive correlation between fatigue severity and functional connectivity of the dorsolateral prefrontal cortex with the rostral inferior parietal lobe (parietal operculum and supramarginal gyrus). Authors recall that the rostral inferior parietal lobe has a role in integrating higher level sensory information and it is involved in maintenance and shifting of attention. An activation likelihood estimation meta-analysis of functional imaging studies on the effect of mental fatigue due to time-on-task on brain activity (Salihu et al., 2022), confirmed the finding that the left inferior parietal lobe was among the regions belonging to the default mode network, showing an increased activity with time-on-task, as well as negative relationship with subjective mental fatigue. A slightly different study, in terms of fMRI paradigm used, is the one by Caseras et al., 2008 which is a mental imagery fMRI study. Authors presented MS patients with different scenarios triggering fatigue (e.g., *Imagine yourself doing your shopping at the*

supermarket and then carrying home heavy bags) or anxiety (e.g., *Imagine yourself sitting in a comfy armchair drinking a nice cup of tea*) and asked them to mentally visualize the scenes and estimate the level of fatigue or anxiety. Authors found that 11 MS patients, as compared to 11 healthy controls, reported feelings of both fatigue and anxiety and, showed increased activation in the occipito-parietal cortex, posterior cingulate gyrus and parahippocampal gyrus, and decreased activation in dorsolateral and dorsomedial prefrontal cortices. Interestingly, controls showed greater activation than MS patients in a cluster with its peak in the superior temporal lobe/lateral sulcus (peak at $x = -51$, $y = -44$, $z = 20$; BA 22/42) which is distant from our cluster of 7 mm in x plane, 6 mm in y plane and 18 mm in the z plane. The task used by authors differs from our paradigm, as in the present study patients are asked to imagine in 1st person perspective the different physical sensations of fatigue, while in the Caseras et al.'s (2008) study imaginable scenes involve several real life scenarios. In addition, in our study, the simple contrasts (SI > Rest, VI > Rest) showed an increased activation in patients vs. controls in the angular gyrus and the cingulate gyrus. This result apparently is similar to Caseras et al.'s (2008) study in terms of an increased activation in the parietal cortex and cingulate gyrus for patients (vs. controls). However, when addressed more in detail, the activation in the angular gyrus, in our study, was due to rest (relative to SI) in controls (relative to patients) and to rest (relative to VI) in controls (relative to patients) and the activation of the cingulate gyrus was due to rest (relative to SI) in controls (relative to patients). Both the angular gyrus and the cingulate cortex are part of the Default mode network. This result reminds of a relation between the Default mode network abnormal activations and multiple sclerosis, e.g., Bonavita et al. (2017).

Our results are consistent with the above-mentioned results on fatigue-related correlates in MS patients, and add further evidence for a role of the left inferior parietal cortex in the pathophysiology of fatigue. At variance with the above-mentioned literature reporting hyper-activations there is literature showing also de-activation of the parietal cortex related to fatigue. For instance, Lim et al. (2010) presented participants with a 20 min psychomotor vigilance test and found reduced cerebral blood flow in the frontal, cingulate, and parietal regions after the task. Similarly, Nakagawa et al. (2013) presented participants with visual and auditory divided-attention tasks with low and high attentional loads and reported deactivation in frontal, temporal, occipital, and parietal cortices due to fatigue. In another study Rocca et al. (2016) found decreased activation in the postcentral gyrus among other areas in fatigue patents (vs healthy controls and non-fatigued patients). In our study, a deactivation of the left inferior parietal cortex was found in MS patients as compared to controls, whereas in the above-mentioned literature, hyper-activation is reported. It can be argued that this can be related to the fMRI paradigm used, namely in the above mentioned literature *mental* fatigue is created by means of highly demanding cognitive tasks, while in the present study the first person mental imagery of the principal manifestations of *fatigue* was triggered. However, given that items to be imagined were balanced as each of the items belonging to the derived subscales (general, physical, emotional, and mental as well as in part vigor), which includes also items from the mental scale, our task it does not fully diverge from the previously cited paradigms of highly demanding cognitive tasks.

Based on the literature on the parallelism between imagery and perception (Djordjevic et al., 2005; Ehrsson et al., 2003; Kobayashi et al., 2004; Stippich et al., 2002; Tomasino et al., 2004; Tomasino et al., 2007; Tomasino et al., 2010; Tomasino et al., 2011; Tomasino et al., 2012a; Tomasino et al., 2012b; Tomasino et al., 2013) it is possible that patients mentally experienced these *fatigue* related sensations. They indeed were significantly slower than controls in rating the vividness for SI (as compared to VI). Studies argued for an attentional hypothesis as the cause of fatigue (Calabrese et al. (2010), see also the model of central fatigue proposed by Chaudhuri and Behan (2000)), or a role of a de-regulated motor control (Pellicano et al., 2010). Our task measured principal manifestations of *fatigue,* and we had no measure of attention-related processing. Therefore we cannot fully disentangle whether our results are related to the hypothesis that fatigue is due to dysfunctions in higher-order aspects of attention-related processing, or rather to dysfunctions in motor control, given the role of the posterior parietal lobe in motor planning and multisensory integration (see also the model of central fatigue proposed by Chaudhuri and Behan (2000)). It can be argued that even if participants were instructed to respond as quickly as possible, the group difference could be due to differences in reading speed. However, despite list of items describing a visual scene of comparable length as the fatigue sensation items, patients and controls significantly differed in reading speed only for SI task, compared to the VI task. If results were due to a reading speed difference, this would have affected reading times for both type of stimuli.

Lastly, we did not find changes in activation in basal ganglia, despite previous literature using functional connectivity analyses (e.g., Hidalgo de la Cruz et al., 2018; Tijhuis et al., 2021) and active fMRI studies (e.g., Specogna et al., 2012; Rocca et al., 2016) showed a central role of thalamus and basal ganglia in the pathogenesis of fatigue in MS. We can speculate that those studies used a ROI approach on the basal ganglia to test for functional connectivity, or, in active fMRI studies motor tasks were employed, which are different paradigms hardly comparable to a mental (sensory) imagery task.

5. Limitation of the study

Our study has some limitation. The sample size is relatively small, thus results need to be further addressed with future studies including bigger sample size.

6. Conclusion

The imagery of fatigue related sensation protocol is a reliable fMRI paradigm to measure the neural correlates of fatigue in patients with MS. The use of this paradigm returned the left parietal lobe hypo-activation as the area found in the Group by task interaction. This result, according to the revised literature, can suggest a de-regulation in multisensory integration rather than in attention network in patients with MS.

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CRediT authorship contribution statement

Barbara Tomasino: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Carolina Bonivento:** Writing – review & editing, Writing – original draft, Data curation. **Simone Dal Bello:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Eleonora Lamon:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Riccardo Garbo:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Gian Luigi Gigli:** Writing – review & editing, Supervision, Conceptualization. **Serena D'Agostini:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Mariarosaria Valente:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Data curation, Conceptualization.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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